EXHIBIT 3

ABBOTT

Abbott Laboratories
North Chicago, Illinois 60064

January 14, 1983

Bureau of Drugs, HFD #120
Document Control Room #10B-34
5600 Fishers Lane
Rockville, Maryland 20857

SPECIAL NEW DRUG APPLICATION
SUPPLEMENT - CHANGES BEING EFFECTED

Re: Depakene (valproic acid) Capsules
NDA 18-081/SNDA-013

Gentlemen:

Submitted herewith in accordance with 21 CFR 314.8(d) is final printed labeling revised to expand the section on WARNINGS with regard to Usage in Pregnancy. An annotated copy is included for your reviewing convenience.

Also, in accordance with 21 CFR 200.5(c)(2), enclosed is an informational letter/envelope sent to approximately 238,000 physicians concerning this important change in the labeling. This mailing started December 6, 1982 and was completed by December 10, 1982.

Sincerely,

EBChappell

E. B. Chappell, Ph.D.
Regulatory Operations
Pharmaceutical Products Division
Telephone (312) 937-6844

EBC/bb

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

Approved; OMB No 57-R0003
Use of this form is prohibited after 5/31/82.

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 314.1)

NOTE: No person shall introduce or deliver for introduction into interstate commerce any new drug unless approval of an application filed pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act has been approved with respect to such drug.

Name of applicant Abbott Laboratories

Address 14th & Sheridan Road, North Chicago, Illinois 60064

Date January 14, 1983

Name of new drug Depakene (valproic acid) Capsules

- ☐ Original application (regulation § 314.1).
- ☐ Amendment to original, unapproved application (regulation § 314.6)
- ☐ Abbreviated application (regulation § 314.1(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 314.6).
- ☒ Supplement to an approved application (regulation § 314.8).
- ☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §201.100 (21 CFR 201.100). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §314.8 of the new-drug regulations.

Attached hereto, submitted in the form described in §314.1(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, and expanded summary and evaluation as outlined in §314.1(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for any new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. *a.* Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

FORM FDA 356H (8/80) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it it is to be advertised or represented, in accord with §201.100 (21 CFR 201.100). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of nay such advertising for a prescription drug (see §310.300 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and control applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper, identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing

history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical method used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §310.3(g), from the batches(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for inital marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §310.3(g) of the new-drug regulations, from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug; *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Drugs and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and in vitro studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or other wise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clincial observations and laboratory examinations made, full information

concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of HEW, 5600 Fishers Lane, Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §310.9 of the new-drug regulations, about related drugs; a bibliography will suffice. Include the evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

h. In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320, Subpart B).

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.
Observe the provisions of §314.8 of the new-drug regulations concerning supplemental applications.

14. [Reserved]

15. The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §6.1 of this chapter.

Abbott Laboratories
(Applicant)

Per E B Chappell /E. B. Chappell, Ph.D.
(Responsible official or agent)

Regulatory Operations, PPD
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Tittle 18, sec. 1001.)

Note: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

(Nos. 5681 and 5682)
01-2275-R10—Rev. Dec., 1982

DEPAKENE®

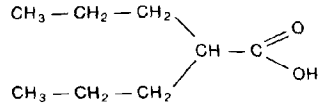
VALPROIC ACID

CAPSULES and SYRUP

WARNING:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING DEPAKENE. THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT WITH DEPAKENE. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, ANOREXIA AND VOMITING. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

DESCRIPTION

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. DEPAKENE has the following structure:



Valproic acid (pKa 4.8) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/ml) and very soluble in organic solvents.

DEPAKENE is supplied as soft elastic capsules and syrup for oral administration. Each capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 ml as the sodium salt.

CLINICAL PHARMACOLOGY

DEPAKENE is an antiepileptic agent which is chemically unrelated to other drugs used to treat seizure disorders. It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs. The mechanism by which DEPAKENE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

DEPAKENE is rapidly absorbed after oral administration. Peak serum levels of valproic acid occur approximately one to four hours after a single oral dose of DEPAKENE. The serum half-life of the parent compound is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption.

Valproic acid is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and variable changes in valproate clearance and elimination.

Elimination of DEPAKENE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta, omega-1, and omega oxidation (C-3, C-4, and C-5 positions). The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

INDICATIONS

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DEPAKENE (VALPROIC ACID) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKENE is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidents usually have occurred during the first six months of treatment with DEPAKENE. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia and vomiting. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKENE to patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO RECENT REPORTS IN THE MEDICAL LITERATURE, DEPAKENE MAY PRODUCE TERATOGENICITY IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY. THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. BASED UPON A SINGLE FRENCH REPORT THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1.2%? THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES

ANIMAL STUDIES HAVE ALSO DEMONSTRATED DEPAKENE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS

Hepatic Dysfunction: See "Contraindications" and "Warnings" sections.

General. Because of reports of thrombocytopenia and inhibition of the secondary phase of platelet aggregation, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If elevation occurs, DEPAKENE should be discontinued.

Since DEPAKENE (valproic acid) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section).

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DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information for Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: DEPAKENE may potentiate the CNS depressant activity of alcohol.

THERE IS EVIDENCE THAT DEPAKENE CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NONRENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF DEPAKENE AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF DEPAKENE AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section).

There have been reports of altered thyroid function tests associated with DEPAKENE. The clinical significance of these is unknown.

Carcinogenesis: DEPAKENE was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day for two years. Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving DEPAKENE and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving DEPAKENE. The actual incidence of fibrosarcomas in male rats was low with only two low dose and five high dose animals being affected. The presence of these tumors is not considered to be drug-related or of biological significance for the following reasons: (1) the overall low incidence, (2) the published variable incidence of spontaneously occurring fibrosarcomas and pulmonary adenomas in rats and mice respectively, (3) the long latency period of the neoplasms and (4) the fact that statistical significance of tumor incidence was present in males only. The significance of these findings for man is unknown at present.

Mutagenesis: Studies on DEPAKENE have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKENE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKENE (VALPROIC ACID) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: See "Warnings" section.

Nursing Mothers: DEPAKENE is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when DEPAKENE is administered to a nursing woman.

ADVERSE REACTIONS

Since DEPAKENE (valproic acid) has usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to DEPAKENE alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See "Drug Interactions" section). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include, as well, increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See "Warnings" section).

Endocrine: There have been reports of irregular menses and secondary amenorrhea occurring in patients receiving DEPAKENE.

Abnormal thyroid function tests have been reported. (See "Precautions" section).

Pancreatic: There have been reports of acute pancreatitis occurring in patients receiving DEPAKENE.

Metabolic: Hyperammonemia. (See "Precautions" section).

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

OVERDOSAGE

Overdosage with valproic acid may result in deep coma.

Since DEPAKENE is absorbed very rapidly, the value of gastric evacuation will vary with the time since ingestion. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of DEPAKENE overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of DEPAKENE it should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKENE (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day, until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

The following table is a guide for the initial daily dose of DEPAKENE (valproic acid) (15 mg/kg/day):

Weight (kg)	Weight (lb)	Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10 - 24.9	22 - 54.9	250	0	0	1
25 - 39.9	55 - 87.9	500	1	0	1
40 - 59.9	88 - 131.9	750	1	1	1
60 - 74.9	132 - 164.9	1,000	1	1	2
75 - 89.9	165 - 197.9	1,250	2	1	2

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum level and therapeutic effect, however, therapeutic serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKENE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See "Precautions" section).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

HOW SUPPLIED

DEPAKENE (valproic acid) is available as orange-colored soft gelatin capsules of 250 mg valproic acid in bottles of 100 capsules (NDC 0074-5681-13), in ABBO-PAC® unit dose packages of 100 capsules (NDC 0074-5681-11), and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt in bottles of 16 ounces (NDC 0074-5682-16).

REFERENCES

1. Robert E., Guibaud, P. Maternal Valproic Acid and Congenital Neural Tube Defects, *The Lancet*, 2(8304):937, 1982.
2. Centers for Disease Control. Valproic Acid and Spina Bifida: A Preliminary Report — France, *Morbidity and Mortality Weekly Report*, 31(42): 565-566, 1982.

ABBOTT LABORATORIES
NORTH CHICAGO, IL60064, U.S.A.

New (Nos. 5681 and 5682)
~~81-2213-R8 Rev Feb. 1982~~

DEPAKENE®

VALPROIC ACID

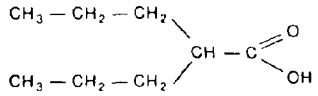
CAPSULES and SYRUP

SPECIMEN

WARNING:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING DEPAKENE. THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT WITH DEPAKENE. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, ANOREXIA AND VOMITING. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

DESCRIPTION

DEPAKENE (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. DEPAKENE has the following structure:



Valproic acid (pKa 4.8) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/ml) and very soluble in organic solvents.

DEPAKENE is supplied as soft elastic capsules and syrup for oral administration. Each capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 ml as the sodium salt.

CLINICAL PHARMACOLOGY

DEPAKENE is an antiepileptic agent which is chemically unrelated to other drugs used to treat seizure disorders. It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs. The mechanism by which DEPAKENE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

DEPAKENE is rapidly absorbed after oral administration. Peak serum levels of valproic acid occur approximately one to four hours after a single oral dose of DEPAKENE. The serum half-life ~~Sh~~ of the parent compound is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption.

Valproic acid is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and variable changes in valproate clearance and elimination.

Elimination of DEPAKENE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta, omega-1, and omega oxidation (C-3, C-4, and C-5 positions). The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

INDICATIONS

DEPAKENE (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKENE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DEPAKENE (VALPROIC ACID) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKENE is contraindicated in patients with known hypersensitivity to the drug.

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WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving DEPAKENE. These incidents usually have occurred during the first six months of treatment with DEPAKENE. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia and vomiting. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKENE to patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of greater incidence of adverse effects.

~~Usage in Pregnancy: THE EFFECTS OF~~ DEPAKENE IN HUMAN PREGNANCY ARE UNKNOWN. ANIMAL STUDIES HAVE DEMONSTRATED TERATOGENICITY.

Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

Usage in Pregnancy: ACCORDING TO RECENT REPORTS IN THE MEDICAL LITERATURE, DEPAKENE MAY PRODUCE TERATOGENICITY IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY. THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. BASED UPON A SINGLE FRENCH REPORT,[1] THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1.2%.[2] THIS RISK IS SIMILAR TO THAT FOR NON-EPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

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ANIMAL STUDIES HAVE ALSO DEMONSTRATED DEPAKENE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

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PRECAUTIONS

Hepatic Dysfunction: See "Contraindications" and "Warnings" sections.

General: Because of reports of thrombocytopenia and inhibition of the secondary phase of platelet aggregation, platelet counts and bleeding time determination are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKENE be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of DEPAKENE dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If elevation occurs, DEPAKENE should be discontinued.

Since DEPAKENE (valproic acid) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section).

DEPAKENE is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

Information for Patients: Since DEPAKENE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

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Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

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Caution is recommended when DEPAKENE (valproic acid) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section).

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North Chicago, Illinois 60064

Dear Doctor:

RE: PREGNANCY AND VALPROIC ACID (DEPAKENE®)

New data concerning the potential teratogenicity of Depakene have recently been brought to our attention by a Letter to the Editor in The Lancet of October 23, 1982. A review of the same data appeared in a bulletin issued jointly by the Food and Drug Administration and the Centers for Disease Control (CDC) in the Morbidity and Mortality Weekly Report of October 29, 1982.

According to these reports, data collected in the Rhone Valley area of France indicate a higher than normal incidence of spina bifida in the offspring of epileptic mothers who received valproate therapy during the first trimester of pregnancy. Based upon this single preliminary report, the CDC has estimated the risk of valproic acid exposed women having children with spina bifida to be approximately 1.2%. This risk is similar to that for non-epileptic women who have had children with neural tube defects. While no confirmatory data have been found in other birth registries, which may be due to the limited number of valproate exposures evaluable in these populations, we nevertheless feel it appropriate to bring this preliminary report to your attention at this time since there are prenatal counseling centers for women who may have an increased risk of having children with spina bifida.

As you are well aware, the fetus of a pregnant epileptic woman is at an increased risk of serious malformation both as a result of the disease itself and because of various anticonvulsant drugs utilized in treatment. All anticonvulsants carry a warning of potential human teratogenicity in their labeling. Some of these drugs, i.e., phenytoin, trimethadione, paramethadione and valproic acid, have now been associated with increased risk of specific congenital defects.

On the basis of the above mentioned preliminary data, we have made certain revisions in the "Use in Pregnancy" section of our Depakene package insert. A copy of this revised insert is included for your information.

Sincerely,

John G Page, M.D.

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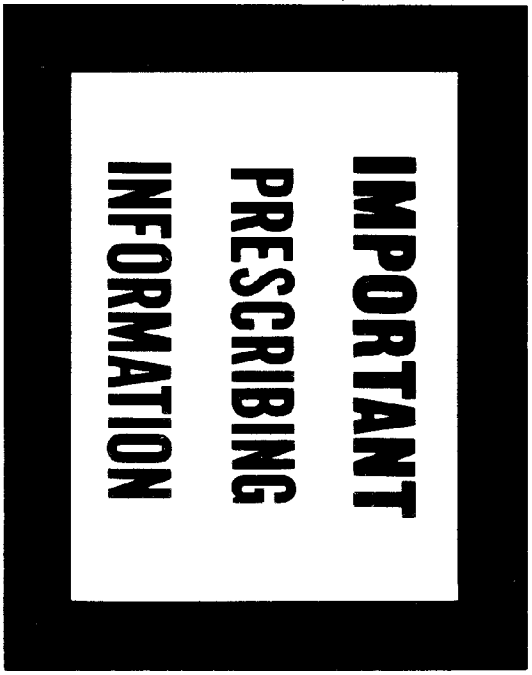
212504—Dec., 1982



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